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TITLE: Implicit Learning Abilities Predict Treatment Response in Autism Spectrum Disorders

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14. ABSTRACT
Intensive early behavioral interventions are the most effective treatment for Autism Spectrum Disorder (ASD), but almost half of the children do not make significant gains. Implicit learning skills are integral to behavioral interventions in ASD. Yet there is inconsistency in the literature as to whether individuals with ASD have difficulties with such learning. In this pilot award, we use multiple levels of inquiry to address implicit learning abilities in a heterogeneous sample of young children with ASD. Preliminary data from the learning task suggests that when data is averaged together from children with ASD and compared to typically developing (TD) children, it appears that children with ASD are not able to learn implicitly. However, while the sample is still small, we have observed individual differences in the expression of learning, with some but not all children with ASD learning on the task. Determining individual variability for learning in ASD is consistent with the primary goal of the project and it is the hope that this information can be used in the future to tailor behavioral interventions for children with ASD.

15. SUBJECT TERMS

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1. INTRODUCTION

Intensive early behavioral interventions are the most effective treatment for Autism Spectrum Disorder (ASD), but almost half of the children do not make significant gains. Implicit associative learning skills are integral to behavioral interventions in ASD and fundamental to the acquisition of social communication and language abilities. Yet there is inconsistency in the literature as to whether individuals with ASD have difficulties with such learning. Some suggest that there is impairment, while others report no differences compared to typically developing individuals. It is likely that the discrepancy is not simply explained by methodological differences across studies, but reflects variability within ASD for implicit learning. We hypothesize that the children who do not respond to classic behavioral intervention have difficulties with implicit learning. If we can identify these children earlier, and develop techniques to overcome these difficulties, then it is possible to optimize their ability to learn, and consequently increase their treatment response. To date, implicit associative learning studies have focused on high functioning, school-aged children and young adults. In this pilot award, we use multiple levels of inquiry to address implicit learning abilities in a heterogeneous sample of young children with ASD. It is the hope that understanding the limitations of implicit learning in ASD has the potential to improve the number of children that respond to behavioral intervention.

2. KEYWORDS

Autism Spectrum Disorder, implicit learning, associative learning, individual differences, functional Magnetic Resonance Imaging (fMRI), Intellectual Developmental Disorder.

3. ACCOMPLISHMENTS

What were the major goals of the project?

There are three goals of the project. The first is to individual differences in implicit learning abilities using behavioral methods in 1) high *and* low cognitively able children with ASD and 2) children with Intellectual Developmental Disorder (IDD) without ASD. The second goal is to perform a pilot study to determine the underlying neural circuitry of implicit learning abilities using functional Magnetic Resonance Imaging (fMRI) in young, more cognitively able children with ASD. The third goal is to perform a pilot study to target a subset of children with ASD who are receiving intensive behavioral treatment to determine whether faster implicit learning abilities predict children's gains in social communication skills.

What was accomplished under these goals?

Testing for the behavioral task (Aim 1) has surpassed target expectations for year 1. As stated in the statement of work (SOW), the target was to enroll 15 individuals and 27 children have completed testing. For the learning task during fMRI the target was to enroll 15 individuals, and while only one child completed the MRI this year, subsequent to the reporting period for year 1, an additional child has completed the MRI and a third is scheduled. We discuss the difficulties and revised strategies for recruiting children with ASD for the MRI experiment below.

Consistent with our experimental goals, the 27 participants with ASD and IDD without ASD we tested have a range of cognitive abilities. The children who performed the learning task had verbal IQ abilities from 56 to 162 and nonverbal IQ abilities from 36 to 134. This large range was a primary objective of the study and it is encouraging that children on the lower end of the cognitive abilities spectrum have been able to complete the learning task on the iPad and also enjoy the task.

Consistent with our hypotheses, we have observed on our learning task that when you average data from children with ASD and compare the data to typically developing (TD) children, it appears that children with ASD are not able to learn implicitly (see Figure 1). In the figure, the two learning conditions from the iPad task are plotted (high probability versus low probability) by trial (1-11). The

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reaction times are converted to z-scores in order to standardize the responses and facilitate comparisons across subjects. A positive z-score is a slower reaction time than average and a negative z-score is a faster reaction time than average. As shown in figure 1 in the left graph, it is clear that by trial 8, the TD children are showing the expected pattern of learning. After seeing repeated presentations of different pairs of images, their reaction times are faster to touch a target after seeing the cue that reliably predicts the target will appear (high probability condition), whereas their reaction times are slower after seeing a cue that does not reliably predict the target will appear (low probability). The graph on the right is the preliminary data from the children with ASD. It is clear that the children with ASD on average do not demonstrate the same pattern of learning as the TD children. There is no clear differentiation in their behavior towards the two different probabilities. As we expected, when data from children with ASD is averaged, it often misses the individual differences and suggests a general deficit that may not be present in all children with ASD.
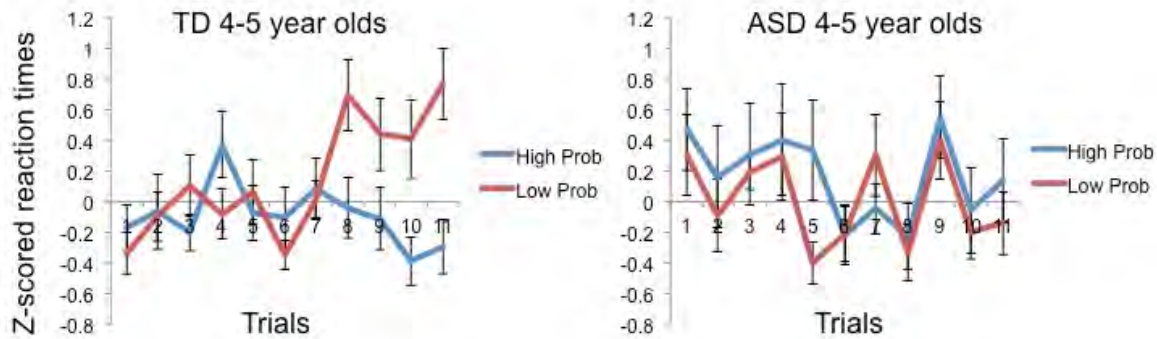

Figure 1: Left panel depicts z-scored reaction times for Typically Developing (TD) children ages 4-5 years for the two learning conditions (High Probability (high prob) versus Low Probability (low prob). Error bars represent standard error of the mean (SEM). The right panel depicts z-scored reaction times for children with Autism Spectrum Disorder (ASD) ages 4-5 years. Positive z-scores represent slower than average reaction times and negative z-scores represent faster than average reaction times. TD children show patterns of learning by trial 8 because they respond faster to targets after seeing high probability cues and slower to targets after seeing lower probability cues. Children with ASD when grouped together do not show a pattern of behavior consistent with learning.

While the sample is still small, we have observed certain individual differences in the expression of learning. First, we test whether children have explicit knowledge about what they learned after they have completed the task. So far, 3 of the children with ASD have had conscious awareness of the probabilities in the task, whereas the remaining children could not articulate any knowledge about the different groupings that they learned on the task. Interestingly, the 3 children were not those with the highest cognitive abilities in the sample nor did they have greater accuracy on the learning task. Given that it is only a few children, we are eager to explore how differences in conscious awareness relate to differences in learning and autism symptoms as the sample increases. The second result that suggests individual differences on the learning task in ASD is that we isolated data from the four children with ASD who have the highest cognitive abilities, and there is evidence that they learn the patterns on the task faster than TD children (see Figure 2). While it is only a few subjects, it appears that their reaction times demonstrate a pattern of learning at trial 3. While the reaction times are no longer differentiated by trial 5 it is possible that they quickly become bored and are no longer paying close attention to the contingencies. Looking for individual variability for when children learn the contingencies on the task is consistent with the primary goal of the project and we will continue to investigate these findings as we increase the sample size.
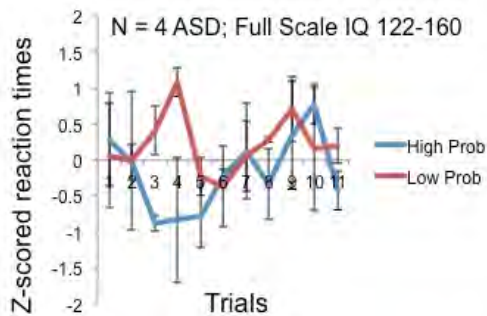

Figure 2: 4 children with ASD with the highest cognitive abilities in the research sample demonstrate a pattern consistent with learning as early as trial 3.

The results from the first year of the study will be presented at the Society for Neuroscience Conference in October 2015 in Chicago, IL. Data on the same behavioral task in the typically developing individuals (controls) was presented at the Society for Neuroscience Conference in November 2014 in Washington DC. Rebecca Jones (co-PI) gave the following presentations about the work: January 2015 to the Sackler Infant Seminar series at Weill Cornell Medical College; May 2015 to Psychiatry Residents at Weill Cornell and May 2015 to the Seaver Autism Center at the Icahn School of Medicine at Mount Sinai.

What opportunities for training and professional development has the project provided?
While training and professional development is not a focus of this autism pilot award, the following activities have occurred in the past year. Catherine Lord (PI) was elected as a member of the Institute of Medicine of the National Academies. Rebecca Jones (co-PI) was promoted to Assistant Professor from Postdoctoral fellow at Weill Cornell Medical College in the Department of Psychiatry.

How were the results disseminated to communities of interest?
The Center for Autism and the Developing Brain (CADB) participates in over a dozen local community events throughout the year and individual clinicians regularly provide information sessions about the services at CADB. For this research project, we recruited families and spread information about our research, at the World Science Festival in Washington Square Park, NY in May 2015 and Rocket Park Recess at the NY Hall of Science in Queens, NY in July 2015.

What do you plan to do during the next reporting period to accomplish the goals?
In order to accomplish the goals and objectives in the next reporting period, we will complete the following: First, in July 2015 with IRB approval, we extended the age range for our brain imaging participants to 9 years of age. In the past year, we had difficulties recruiting participants who were willing to complete the MRI. We are optimistic that slightly older children will be more willing to complete the MRI procedures and that we will also obtain better quality data as older children move less during the MRI. We fully anticipate completing 15 MRI scans by August 2016. Second, we will begin testing for Aim 3, where we will target a subset of children with ASD who are receiving therapy at our clinic, the Center for Autism and the Developing Brain (CADB). Children will be targeted prior to enrolling in a social skills group, one-on-one speech, occupational and/or physical therapy and enrolled in the study. Each child will complete the learning task on an iPad as well as the Brief Measurement of Social Communication skills Change (BOSC-C), to measure social communication abilities during a semi-structured naturalistic play interaction. After three months of therapy, the child will complete the same behavioral and social communication skills procedures. We will measure if there are performance changes on the learning task that correspond to changes observed on the BOSC-C. Third, we will complete testing on the iPad in both children with ASD as well as those with Intellectual Developmental Disorder (IDD), particularly targeting children who are less cognitively able.

4. IMPACT
What was the impact on the development of the principle discipline of the project?
The pilot data we have collected thus far is from a small sample of subjects, so it is difficult to draw well-defined conclusions from the results. However, it is clear that there is individual variability in how children with ASD learn and that the learning task on the iPad is sensitive to detecting these differences. Moving beyond averaging large groups of children with ASD, but rather detecting individual differences is important for understanding whether we can predict how children with ASD will respond to behavioral interventions. The goal of aim 3, which we will address in year 2, is if differences in learning on the iPad task are consistent with treatment changes. We predict the children who fail to respond to behavioral intervention have implicit learning difficulties. The earlier we can identify these children, the more likely it is to optimize their learning abilities and thus improve

their response to behavioral treatment.

What was the impact on other disciplines?
Nothing to report.
What was the impact on technology transfer?
Nothing to report.
What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS
Changes in approach and reasons for change/Actual anticipated problems or delays and actions or plans to resolve them
As discussed above, we experienced delays in recruiting children with ASD to complete the MRI. While the initial SOW intended for all 15 individuals to complete the MRI during year 1, we plan to complete the remaining subjects in year 2. With IRB approval, we extended our age range by 2 years of age for the MRI participants in order to increase the range of participants that we were able to recruit. The 2 year age range increase does not impact the scope of the science.

Changes that had a significant impact on expenditures
We have unused funds that were designated for MRI scanning and compensating scanning subjects in year 1 and thus request a carry forward to year 2.

Significant changes in use or care of human subjects, vertebrate animals, biohazards and/or select agents
There were no other changes in approach or changes that impacted use or care of human subjects.

6. PRODUCTS

Conference Presentations
Jones, RM., Carberry, C., Dellarco, D., Hamo, A., Lord, C. Implicit learning in young children with autism. To be presented at the Society for Neuroscience annual meeting, Chicago, IL. October 2015.

Book Chapter
DiMartino, A., Jones, R.M., Choi, E.Y., Haber, S., & Castellanos, F.X. (*in prep*). Autism and the Striatum. In *Autism Imaging and Devices*.

7. PARTICIPANTS AND OTHER COLLABORATORS
What individuals have worked on the project?
Name: **Catherine Lord**
Project Role: Principle Investigator

Research Identifier: CELORD (era commons user name)

Nearest person month worked: 0.4 months

Contribution to Project: Dr. Lord has overseen the project. Specifically, she supervised the design of the learning task, data collection and preliminary analyses. She meets regularly with Dr. Jones about all aspects of the experiment and provides guidance about issues that arise.

Funding Support:
R01MH104423-02 Wetherby (PI) Lord (WCMC PI)   7/1/14 – 6/30/19
NIMH   0.96 CM
Mobilizing Community Systems to Engage Families in Early ASD Detection & Services

R01 HD073975-04 Kasari (PI) Lord (WCMC PI)   9/4/12-5/31/2017
NICHD   1.2 CM
Adaptive Interventions for Minimally Verbal Children with ASD in the Community

RFA 336363 Lord (PI)   7/1/14-11/30/15
Simons Foundation   1.8 CM Ext
Advancing a Standardized Research Protocol to Study Treatment Effects in Individuals with Autism Spectrum Disorder

UL1TR000457   Lord (Site PI)   7/1/14-6/30/16
NCATS   0.06 CM
Training Selective Auditory Attention in People with Autism

12IPA1203268 Lord (PI)
Center for Disease Control   3/1/15-12/31/15
Consultant to Autism Projects   0.12 CM
This consultation is regarding diagnosis in CDC epidemiological studies of autism.

R01HD081199-01A1 Lord (PI)   9/1/15-5/31/20
NICHD   2.4 CM
Transitioning to Adulthood: A Prospective Longitudinal Study

SFARI Research Award RFA Lord (PI)   9/1/15-8/31/18
Simons Foundation   1.2 CM
Developing Scalable Measures of Behavior Change for ASD Treatments

Name: **Rebecca Jones**
Project Role: Co-Principle Investigator

Research Identifier: REJ2004 (era commons)

Nearest person month worked: 8.2 months

Contribution to Project: Dr. Jones has performed all of the practical components of the research. She is in charge of maintaining the IRB, recruiting participants, collecting data from all of the research subjects and is responsible for performing analyses.

Funding Support:

RFA 336363 Lord (PI)   7/1/2014–11/30/2015
Simons Foundation   3.24 CM Ext.
Advancing a Standardized Research Protocol to Study Treatment Effects in Individuals with Autism Spectrum Disorder
Role: Co-Investigator

Name: **BJ Casey**
Project Role: Co-Investigator

Research Identifier: BJCASEY (era commons)

Nearest person month worked: 0.3 months

Contribution to Project: Dr. Casey supervised the adaptation of the learning task on the iPad for the MRI environment. She meets regularly with Dr. Jones to discuss issues as relates to recruitment, data collection and analysis for the MRI data. While Dr. Casey will not receive funding for year 2, she has a standing bi-monthly meeting with Dr. Jones about the project, and is committed to providing support and guidance through year 2.

Funding Support:

R01 HD069178 (Ochsner PI) (Casey WCMC PI)   9/28/2010-7/31/2015
NICHD   1.2 CM
Development of Emotion Regulation Mechanisms impacting Health

Multisite Project (Casey)   7/01/2012-6/30/2016
MacArthur Foundation   .6 CM Ext. Year
Adolescent Decision Making related to Criminal Activity

R01DK097399 (Rosenbaum/Mayer PI) (Casey WCMC PI)   9/18/2013-8/31/2015
NIDDK   1.2 CM
Functional imaging and eating behavior among FTO genotypes in pre-obese children

1 R21 MH103650-01 (Broft PI) (Casey WCMC PI)   4/1/2014-5/31/20
NIMH   1.2 CM
Impact of negative affect on neural circuitry in bulimia nervosa: an fMRI study

Has there been a change in active other support of the PD/PI(s) or senior key personnel since the last reporting period?

What other organizations were involved as partners?
No other organizations were involved as partners.

8. SPECIAL REPORTING REQUIREMENTS